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Mixed Protamine Human Insulin Injection (30R)

DRUG NAME

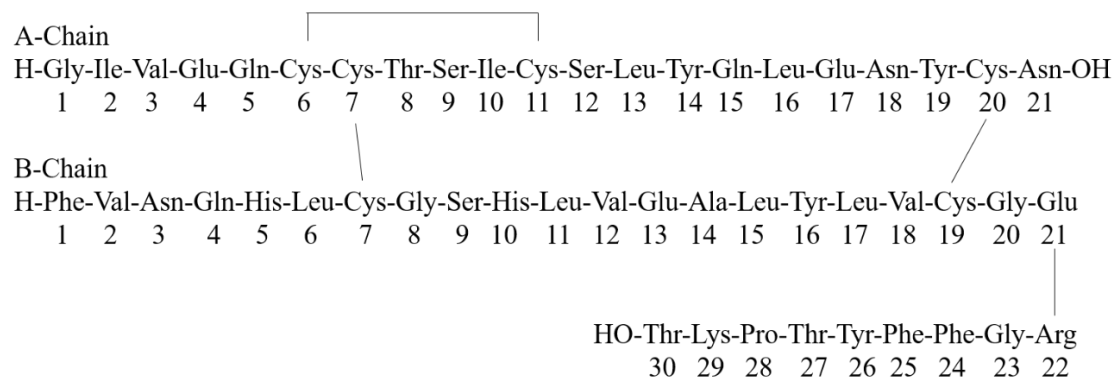
Generic name: Mixed Protamine Human Insulin Injection (30R)

COMPOSITION

Active ingredient: 30% soluble human insulin and 70% protamine human insulin.

Chemical name: human insulin

Chemical structural formula:



Molecular formula: $C_{257}H_{383}N_{65}O_{77}S_6$

Molecular weight: 5807.69 Da

Excipient: Zinc chloride, Phenol (0.65 mg/ml), M-cresol (1.6 mg/ml), Glycerol, Disodium hydrogen phosphate, Protamine sulfate, Hydrochloric acid or Sodium hydroxide (for pH adjustment), Water for injections

DESCRIPTION

Mixed Protamine Human Insulin Injection (30R) is a white or almost white suspension, and should be evenly resuspended after shock.

INDICATION

Mixed Protamine Human Insulin Injection (30R) is indicated to improve glycemic control in diabetic patients who need insulin treatment.

STRENGTHS

100 units per mL

DOSAGE AND ADMINISTRATION

Mixed Protamine Human Insulin Injection (30R) is a two-phase insulin preparation, including short-acting insulin and intermediate-acting insulin.

Premixed insulin is usually given once or twice daily when it is necessary to take effect quickly and prolong the effect.

Dosage

The dosage should be determined by the doctors according to the patients' condition. The dose is usually between 0.3-1.0 U/kg/day. When there is insulin resistance in the patients, such as adolescence or obesity, the daily insulin dose may be increased. When there is residual endogenous insulin secretion in patients, the daily insulin dose may be reduced.

Good glycemic control in diabetic patients can effectively delay the occurrence of late complications of diabetes. Therefore, close metabolic monitoring is recommended.

Eat a meals or sack containing carbohydrates within 30 minutes after injection.

Mixed Protamine Human Insulin Injection (30R) should only be administered subcutaneously. Under no circumstances can this product be administered by intravenous infusion.

Administer in the subcutaneous tissue of the thigh, upper arm, buttocks, or abdominal wall. Rotate injection sites, and the same injection site should not be injected more than once a month.

Be careful when injecting this product subcutaneously, and do not inject the liquid into the blood vessel. After the injection, do not squeeze and rub the injection site. Patients must be educated to use syringes correctly.

For different individuals or different times of the same individual, the duration of action is different. Therefore, as with all insulin preparations, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Instructions for use

(a) Before injection

Before use, gently roll the refill between the palms of your hands at least 10 times, and carefully invert the refill at 180° at least 10 times until the solution is uniform turbidity or emulsion. If not, repeat the above actions until it is mixed evenly. The small glass beads inside the refill help to mix the drug solution. Do not shake vigorously, otherwise the foam produced will affect the accurate measurement of the dose.

Always check the refill. Do not use if lumps or white particles similar to "frost" bonded to the bottom or wall of the bottle are seen.

The design of this refill does not allow any other insulin to be mixed into the refill. The disposable pen can only be used once, and cannot be refilled again.

The following is only an overview. The instructions attached to each insulin injection pen must be strictly followed when installing the refill, needle and insulin injection.

(b) Injection

1. Wash your hands before injection;
2. Choose your injection site;
3. Clean the skin of the injection site as required;
4. Pull off the cap of the needle;
5. Smooth and tighten the skin at the injection site by hand, gently pinch it up, and inject subcutaneously according to the operation instructions;
6. Press the button;
7. Pull the needle out of your skin, press the injection site gently for a few seconds. Do not rub the area.
8. After the injection, use the needle cap to disassemble the needle, and dispose it properly;
9. Rotate injection sites, and the same injection site should not be injected more than once a month.

ADVERSE REACTIONS

Hypoglycemia is the most common adverse reaction associated with insulins. The hypoglycemia symptoms include cold sweats, pallor and chills, fatigue, nervousness or tremors, anxiety, unusual tiredness or weakness, inattention, drowsiness, excessive hunger, abnormal vision, headache, nausea, and palpitations. Severe hypoglycemia can cause loss of consciousness and/or convulsion, temporary or permanent brain function damage and even death.

The following related adverse reactions are listed below by incidence and in order of system organ class. The frequency of incidence is classified in the following manner: very common: $\geq 1/10$; common: $\geq 1/100$ to $< 1/10$; uncommon: $\geq 1/1,000$ to $< 1/100$; rare: $\geq 1/10,000$ to $< 1/1,000$; very rare: $< 1/10,000$; and not clear (difficult to evaluate based on available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness:

Immune system disorders

Uncommon – urticaria, rash

Very rare – anaphylactic reactions

Symptoms of systemic anaphylaxis include systemic rash, pruritus, sweating, gastrointestinal discomfort, angioneuroedema, dyspnea, palpitation, decreased blood pressure, and dizziness or loss of consciousness. Systemic allergic reactions can be life-threatening.

Immunogenicity

As with all therapeutic peptides, insulin administration may cause anti-insulin antibodies to form.

Nervous system disorders

Uncommon – peripheral neuropathy

Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible.

Eye disorders

Very rare – refraction disorders

At the beginning of the insulin treatment, refraction anomalies may occur. This reaction is usually of a transitory nature.

Uncommon – diabetic retinopathy

Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy, while intensification of insulin therapy with abrupt improvement in glycemic control may be associated with temporary worsening of diabetic retinopathy.

Skin and subcutaneous tissue disorders

Uncommon – lipodystrophy

Lipodystrophy may occur at the injection site. This situation is usually caused by multiple injections at the same site without proper rotation of injection sites in the injection area.

Localized Cutaneous Amyloidosis

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

General disorders and administration site conditions

Uncommon – injection site reactions

During insulin treatment, injection site reactions (redness, swelling, itching, pain and bruising) may occur. These reactions are usually of a transitory nature.

Uncommon – oedema

At the beginning of the insulin treatment, oedema may occur. These reactions are usually of a transitory nature.

Metabolism and nutrition disorders

Hypokalemia

All insulin products, including Mixed Protamine Human Insulin Injection (30R), cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Investigations

Weight gain

Weight gain has occurred with some insulin therapies including Mixed Protamine Human Insulin Injection (30R) and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

CONTRAINDICATIONS

During episodes of hypoglycemia.

In patients who have had hypersensitivity reactions to Mixed Protamine Human Insulin Injection (30R) or any of its excipients.

PRECAUTIONS

- Under no circumstances can mixed human insulin be administered by intravenous infusion.
- Never share a syringe with another person. Sharing poses a risk for cross infection.
- Check whether the product is intact before use (e.g. no cracks). Do not use it if any damage is seen.
- After each injection, be sure to remove the needle. Otherwise the liquid may leak out when temperature changes, which can cause inaccurate dosing.
- Do not refill for use.
- Cannot be used in insulin infusion pumps.
- Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, intermediate-acting, long-acting, etc.), origin (animal insulin, human insulin analogue) and/or method of

manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dose.

- Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, intensification of insulin therapy, in patients with diabetic nerve disease, in patients using medications such as β -blockers.
- Symptomatic awareness of hypoglycemia may be less pronounced or different from the past in patients who switch from animal derived insulin to this product. Failure to correct hypoglycemia or hyperglycemia in time can lead to loss of consciousness, coma and even death.
- Inadequate dosing or discontinuation of treatment, especially in insulin dependent diabetes mellitus, may lead to hyperglycemia and diabetic ketoacidosis. Usually, the first symptoms of hyperglycemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. Diabetic ketoacidosis is a potential lethal factor.
- Renal impairment may reduce the patient's insulin requirements.
- Due to gluconeogenesis and the decline of insulin decomposition ability, when hepatic impairment, the insulin requirements must be reduced. However, in patients with chronic hepatic impairment, insulin resistance increases, so the insulin requirements may increase accordingly.
- Insulin requirements may be increased when the patient is suffering from other diseases or mood changes.
- When patients increase exercise or change their diet, the insulin requirements need to be adjusted accordingly. Exercise immediately after meals increases the risk of hypoglycemia.
- Thiazolidinediones (TZDs) used in combination with insulin

Cases of congestive heart failure have been reported when TZDs are used combined with insulin, especially for patients with risk factors for development of congestive heart failure. This should be kept in mind if treatment with the combination of TZDs with insulin is considered.

When TZDs are used in combination with insulin, signs and symptoms of congestive heart failure such as weight gain and oedema should be observed. If any deterioration in cardiac symptoms occurs, pioglitazone should be discontinued.

In clinical trials of rosiglitazone plus insulin, rosiglitazone increased the risk of congestive heart failure. So rosiglitazone combined with insulin is not recommended.

- **Effects on ability to drive and use machines**

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia.

This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in these circumstances.

- **Athletes should use with caution.**

PREGNANCY AND LACTATION

There are no restrictions on treatment of diabetes with insulin during pregnancy, because insulin does not pass the placental barrier.

Both hypoglycemia and hyperglycemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death in utero. Intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy.

Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters.

After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

There is no restriction on treatment with insulin during lactation. Insulin treatment of the nursing mother presents no risk to the baby. However, the insulin dose may need to be adjusted.

PEDIATRIC USE

The pharmacokinetic characteristics of this product in children and adolescents are basically the same as those in adults. See **DOSAGE AND ADMINISTRATION** for details.

GERIATRIC USE

The main purpose of insulin treatment for elderly patients is to reduce symptoms and avoid hypoglycemia. See **DOSAGE AND ADMINISTRATION** for details.

DRUG INTERACTIONS

A number of medicinal products are known to interact with glucose metabolism. Therefore, doctors should ask about all drugs currently taken by patients and consider possible drug interactions.

The following substances may reduce the patient's insulin requirement:

oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), non-selectivity β -blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.

The following substances may increase the patient's insulin requirement:

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, β -sympathomimetics, growth hormone and danazol.

β -blockers may mask the symptoms of hypoglycemia and prolong its recovery time.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or prolong the hypoglycemic effect of insulin.

Incompatibility

Insulin suspensions are not to be used in insulin infusion pumps.

OVERDOSAGE

Because blood glucose concentration is determined by insulin level, glucose utilization and other metabolic factors, there is no strict definition of insulin excess. Insulin overreaction caused by food intake and energy consumption can lead to hypoglycemia.

The symptoms of hypoglycemia may include tiredness, blurred consciousness, palpitation, sweating, vomiting, headache and so on.

Mild hypoglycemic episodes can be treated by oral administration of glucose, sugar or sugary products.

Severe hypoglycemic episodes can be treated with glucagon given intramuscularly or subcutaneously. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse. Glucose must be given intravenously, if the patient does not respond to glucagon.

When the patients become unconscious, glucagon should be given intramuscularly or subcutaneously immediately. Glucose must be given intravenously, if the patient does not respond. Upon regaining consciousness, feed the patients immediately.

Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

PHARMACODYNAMICS

Mixed protamine human insulin injection is a human insulin analog produced by recombinant DNA technology, and its structure and function are the same with natural insulin. It can regulate glucose metabolism, promote the uptake and utilization of glucose in liver, bone and adipose tissue, promote the transformation of glucose into muscle glycogen and hepatic glycogen, and inhibit gluconeogenesis, so as to reduce blood glucose.

Injecting diabetic patients with appropriate doses of insulin while controlling diet and exercise can temporarily restore the patients' ability to metabolize carbohydrates, fats and proteins, and promote

the storage of hepatic glycogen and the conversion of glucose into fat. Administering appropriate doses of insulin to diabetic patients at appropriate intervals can maintain blood glucose within a reasonable range, avoid the appearance of urinary glucose and ketone, and prevent the occurrence of diabetic acidosis and coma.

PHARMACOKINETICS

Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics. This process is influenced by several factors (e.g. insulin dose, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin are therefore affected by significant intra- and inter-individual variation.

Absorption – The product is a mixture of fast-acting insulin and long-acting insulin, so it has the characteristics of rapid and slow absorption at the same time. The maximum plasma concentration of the fast-acting insulin is reached within 1.5-2.5 hours after subcutaneous administration.

Distribution – No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.

Metabolism – It is reported that human insulin can be degraded by insulin protease or insulin-degrading enzymes and possibly protein disulfide isomerase. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed, none of the metabolites formed following the cleavage are active.

Elimination - The half-life is determined by the rate of absorption from the subcutaneous tissue. The half-life is therefore a measure of the absorption rather than of the elimination of insulin from plasma (insulin in the blood stream has a half-life of only a few minutes). Trials have indicated a half-life of about 5-10 hours.

STORAGE

Not in-use – Store at 2-8°C, but not in the freezer. Protect from heat and light.

In-use – Do not store in a refrigerator. Can store at room temperature (below 30°C) for 4 weeks, and the pen must be discarded after 4 weeks.

After refills are loaded into the injection pen, do not store with the needle.

Store carefully, and keep out of the reach of children.

PACKAGE

Cartridge (refill), compound aluminum cap, brominated butyl rubber stopper, glass bead (for mixing)

Packing specification: 1 cartridge/box

SHELF LIFE

24 months

MANUFACTURER

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